REMARKS

I. Status of the Claims

Claims 1-35 were originally filed. Claims 11 and 22-30 were withdrawn as the result of a restriction requirement and are hereby canceled. New claims 36 and 37 are added, support for which can be found in the specification and in original claims 6 and 17.

Independent claims 1 and 12 are amended to recite "pancreatic cells" in place of "endocrine pancreas β-cells." This amendment is supported by the specification, *e.g.*, on page 10, lines 13-15. No new matter is introduced.

Upon entry of the present amendment, claims 1-10, 12-21, and 31-37 remain under examination.

II. Priority

The Examiner inquired whether Applicants intend to claim priority to the "related" U.S. Patent Application No. 09/522,376 (the '376 application). Applicants do not intend to claim priority of the present application to the '376 application. The reference to the '376 application as a "related" application has been deleted. The statement of incorporating the '376 application has been moved to a different location of the present application.

III. Claim Rejections

A. 35 U.S.C. §112, First Paragraph

Claims 10 and 21 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description. Specifically, the Examiner asserted that the βlox5 cells required for practicing the presenting invention do not appear readily available or obtainable by a repeatable method set forth in the specification. Applicants respectfully traverse the rejection.

The βlox5 cells are indeed readily available to the general public, as the deposit information is provided on page 4, lines 6-8, of the present specification:

> A deposit of the βlox5 cells, which are human pancreatic cells, was made on July 19, 2001 under accession number PTA-3532

at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209.

Applicants further attach a declaration under 35 U.S.C. § 1.132 by Dr. Fred Levine, a named inventor on this application (Exhibit A). This Declaration was originally filed on October 22, 2001, for USSN 09/522,376, now U.S. Patent No. 6,448,045, issued September 10, 2002, and attests that the βlox5 cell line was deposited with the ATCC and that all restrictions on the availability to the public of the cell line will be removed upon issuance of a patent for the '376 application.

In light of the forgoing, Applicants submit that a sufficient showing has been made to establish the proper deposit and availability of the βlox5 cells. The withdrawal of the written description rejection is respectfully requested.

B. 35 U.S.C. §102

Claims 1-6, 12-17, 31, and 32 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Egan *et al.* (WO00/09666). Applicants respectfully traverse the rejection in light of the present amendment.

To anticipate a pending claim, a reference must provide every element of the claim. MPEP §2131. As will be discussed below in more detail, the Examiner has not shown that the Egan reference contains all elements of the rejected claims. Specifically, Applicants contend that for claims 1-6 and 12-17, the element of culturing cells in cell-cell contact is not found in the reference; and that for claims 6, 17, 31, and 32, the element of culturing co-transfected β-cells is not present in the reference.

To establish anticipation, the Examiner first set forth five specified cell culture conditions and asserted that any culture conditions that meet these specific requirements to meet the limitation of "under conditions such that the β-cells are in contact with other cells in the culture." *See*, the paragraph bridging pages 6 and 7 of the Office Action mailed October 2, 2003. These five conditions are:

1. Growing cells in suspension such that they form three dimensional aggregates, such as on a plate coated with a hydrogel that prevents the cells from adhering to the bottom of a dish;

2. Growing cells in an incubator typically set to 37 degrees Celsius;

3. Growing cells under constituents where the CO_2 concentration is between 1-10%, and preferably 5%;

4. Growing cells in DME, RPMI, 1640, DMEM Iscove's complete or McCoy's Medium; and

5. Including a 5-20% solution of human, horse, calf or bovine fetal serum.

The Examiner then cited various portions of the Egan *et al.* reference to show that all limitations of the pending claims are present in the reference. The paragraph on page 22, lines 11-25, of Egan *et al.* was cited as the teaching of co-transfection of cells with NeuroD/BETA2 and IDX-1. The section on page 4, lines 5-9, of Egan *et al.* was cited as the teaching of using GLP-1 to induce insulin production. Based on the cell culture conditions (particularly the use of 12-well cluster dishes) described in Example 4 on page 43, lines 9-17, of Egan *et al.*, the Examiner cited this section as the teaching of culturing cells in contact with other cells. The Examiner concluded that all elements of claims 1-6, 12-17, and 31-32 are present in Egan *et al.* and these claims are thus anticipated. Applicants respectfully disagree with the Examiner.

(a) Egan et al. Does Not Teach Or Suggest Culture Conditions That Result In Cell-To-Cell Contact

Applicants respectfully submit that the cited reference does not teach or suggest conditions to allow for cell-to-cell contact as recited in the pending claims.

Of the five cell culture conditions referred to by the Examiner, four do not necessarily result in cell-to-cell contact. Only growing cells in three-dimensional aggregates necessarily result in cell-to-cell contact. Egan *et al.* does not teach or suggest growing cells as aggregates.

The Examiner only appears to refer to one paragraph of Egan *et al.* to allegedly demonstrate that the reference describes conditions of cell-to cell contact. *See*, Office Action, page 7. Applicants dispute the Examiner's unsupported assertion that the 12-well cluster cell culture dishes used in Example 4 of the Egan reference "are known to comprise a hydrogel to prevent cells from adhering to the dish, causing them to grow in suspension" and thus form aggregates (last paragraph on page 7 of the October 2, 2003, Office Action).

The Examiner has not cited any evidence that "cluster wells" necessarily contain hydrogel. In the attached Exhibit B, a printout of tissue culture dishes available through Myriad Industries, Applicants note that the Costar 6, 12, 24, 48, or 96-well Cell Culture Clusters are treated for optimal cell attachment, *i.e.*, do not have hydrogel. Hydrogel is found in a different type of plates, Costar Ultra Low Attachment Plates, which are used for culturing cells in suspension. These dishes for suspension culture are not called "cluster" dishes or plates. Because of the lack of explicit description of hydrogel in the 12-well cluster dishes in the Egan reference and particularly in light of evidence to the contrary as shown in Exhibit B, Applicants respectfully submit that the Examiner was incorrect in his unsubstantiated conclusion regarding the presence of hydrogel in the 12-well cluster dishes in Egan's Example 4. Accordingly, Applicants respectfully request withdrawal of the rejection.

(b) The Elements of the Pending Claims Are Not Present in the Egan Reference in a Logical Context

Even if the Examiner's assertion regarding cell-cell contact and culture conditions were correct, **and** the cluster dishes described in Example 4 of the Egan reference did always contain hydrogel to support cell aggregates, Egan *et al.* still does not teach or suggest all elements of the pending claims because the Egan reference does not specifically present all elements of the pending claims together.

For instance, the teaching of GLP-1 induced insulin production, which the Examiner cited on page 4, lines 5-9, of the Egan reference, is provided in the context of describing the state of prior art. The teaching of transfection of NeuroD/BETA2 and IDX-1 (for which the Examiner cited page 22, lines 11-25, of the Egan reference) is provided as a part of a

general description in which NeuroD/BETA2, IDX-1, and E27 are indicated as important for insulin secretion. This description only briefly states that one or more of the three genes may be transfected into non-insulin producing cells. There is no specific reference to the co-transfection of NeuroD/BETA2 and IDX-1 among all possible combinations of the three genes (e.g., as better than E27 alone, NeuroD/BETA2 alone, IDX-1 alone, E27 and NeuroD/BETA2 together, IDX-1 and E27 together, etc.).

Furthermore, the cell culture conditions that the Examiner asserted to be equivalent to culturing cells in cell-cell contact are a part of Example 4 that demonstrates the effects of GLP-1 on AR42J cells. The AR42J cells in Example 4 were neither transfected with NeuroD/BETA2 and IDX-1, nor shown to express insulin gene upon GLP-1 induction. Example 4 simply has no obvious or logical connection with the earlier discussions about transfection of NeuroD/BETA2 or IDX-1. These separate discussions have no immediate connection and are merely present in the same PCT application, more than 20 pages apart. Thus, the limitations of pending claims 1 and 12 (as well as their dependent claims) are not present in such a manner in the Egan reference that they can be reasonably combined.

(c) Egan et al. Does Not Teach Or Suggest The Use Of Beta Cells

Claims 6, 17, 31, and 32 contain the following elements: a **β-cell** that comprises

1. A recombinant PDX-1 polynucleotide; and
2. A recombinant NeuroD/BETA2 polynucleotide.

The Examiner cited the paragraph on page 22, lines 11-25, of Egan *et al.* as the teaching co-transfection of cells with PDX-1 and NeuroD/BETA2. As noted above, this paragraph discusses the possible transfection of one or more of NeuroD/BETA2, IDX-1, and E27 into non-insulin producing cells to induce insulin production, but does not expressly teach the transfection of the combination of NeuroD/BETA2 and IDX-1 genes into the cells. Nor does this paragraph describe or suggest the use of pancreatic β-cells for transfection. The AR42J cells (which are rat pancreas exocrine tumor cells used as a model of acinar tissue) mentioned in Example 4 and other places in the reference are not β-cells. Applicants invite the Examiner to

indicate where Egan *et al.* teaches that β-cells are to be transfected with PDX-1 and NeuroD/BETA2. Therefore, it remains to be shown that all elements of claims 6, 17, 31 and 32 are present in the Egan reference.

In summary, the Egan *et al.* reference does not provide all limitations of the pending claims for the purpose of establishing a basis for an anticipation rejection. Furthermore, nowhere in the Egan reference can any suggestion or motivation, explicit or implied, be found for one of skill in the art to combine the limitations of the pending claims. Applicants therefore respectfully request that the Examiner withdraw the anticipation rejection.

C. 35 U.S.C. §103

Claims 7, 8, 18, 19, 33, and 34 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Egan *et al.* in view of Levine *et al.* Claims 9, 20, and 35 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Egan *et al.* in view of Levine *et al.* and further in view of Baetge *et al.* Applicants respectfully traverse the rejections.

To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art references must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to combine the limitations; third, there must be a reasonable expectation of success in combining the limitations. MPEP §2143.

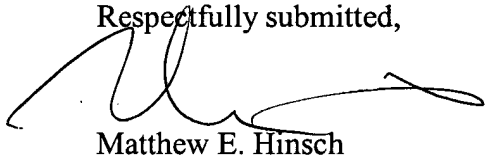
As discussed above, it has not been established that the Egan *et al.* reference teaches or suggests the specific combination of all limitations of independent claims 1, 12, and 31. Indeed, those of skill in the art would not be motivated, upon reading the Egan *et al.* reference, to culture pancreatic cells or co-transfect β-cells as described in the present claims. As far as the other two cited references are concerned, neither Levine *et al.* nor Baetge *et al.* address these gaps in Egan *et al.* Therefore, neither the Levine reference nor the Baetge reference, alone or in combination with Egan *et al.*, supplies any limitations of the independent claims. Accordingly, Applicants therefore submit that no *prima facie* case of obviousness has been established and respectfully request the withdrawal of the obviousness rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Matthew E. Hinsch
Reg. No. 47,651

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300

Attachment: Dr. Levine's Declaration (Exhibit A); printout of description of tissue culture dishes (Exhibit B)
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